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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,915	08/20/2001	Paul R. Odgren	07917-120001 / UMMc-34 Tr	7747

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,915	ODGREN ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-14 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08/20/2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/28/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group 5 and SEQ ID NO:3 in the reply filed on 09/30/2005 is acknowledged. Claims 1-29 are currently pending, and claims 9-14 and 20 are the subject of this Office Action. This restriction is deemed proper and is therefore made FINAL.

Priority

The Examiner has concluded that the subject matter defined in this application is not supported by the provisional application in the chain of priority, 60/933,915, because the provisional application did not disclose SEQ ID NO:3 of the instant application. Therefore, the instant application has an effective filing date of 08/20/2001.

Should the applicant disagree with the examiner's determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 08/20/2001 which specifically supports the particular claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled prior to 08/20/2001.

Information Disclosure Statement

The Information Disclosure Statement was received on 02/28/2002 and has been fully considered by the Examiner.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The election of claims 9-14 and 20 have drawn the application to methods of regulation of TRANCE proteins.

The following title is suggested: Methods of TRANCE regulation of chondrocyte differentiation.

Claim Objections

Claims 12 and 13 are objected to for reciting non-elected subject matter. The Applicant's response to the restriction requirement has resulted in an election of SEQ ID NO: 3. Claims 12 and 13 recite the non-elected subject matter of SEQ ID NO: 4-8.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-14 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TRANCE-increasing agents such as full-length TRANCE polypeptides, full-length TRAF6 polypeptides, and the polypeptide defined by SEQ ID NO: 3, does not reasonably provide enablement for any other TRANCE-increasing agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 9, 10, and 14 are discussed below. Claims 11-13 and 20 are rejected for depending from rejected base claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

1. Claim 9 is drawn to a method of treating a mammal by administering a tumor necrosis factor-related activation-induced cytokine (TRANCE)-increasing agent. While the specification is enabling for several TRANCE-increasing agents, including the full-length human or murine TRANCE polypeptide, TNF-domain containing polypeptides, the polypeptide of SEQ ID NO: 3,

and TRAF6 polypeptide, the breadth of the claim is excessive because the specification does not teach all possible TRANCE-increasing agents. The claim reads broadly on any agent capable of increasing TRANCE, which could be any protein capable of increasing TRANCE levels or activity. Additionally, specific cellular stimuli could also result in increased TRANCE mRNA transcription and protein levels. Examples of stimuli of this type could include cytokine stimulation, stimulation through cell membrane-bound ligands present on other cells, or stimulation by drugs or other pharmaceutical agents. Thus, the specification does not provide guideance for, or provide working examples of every possible TRANCE-increasing agent. It would not be predictable to one of ordinary skill in the art to determine which molecules are TRANCE-increasing agents that can be used with the present invention, and it would require undue experimentation on the part of the skilled artisan to identify such molecules or stimuli, and determine their effectiveness in treating bone/cartilage disease. Therefore, because of the excessive breath of the claim, and the unpredictability of the invention, a trained artisan would require undue experimentation to use the invention commensurate with the scope of claim 9.

2. Claims 10 and 14 are drawn to a method of administering a TRANCE-increasing agent comprising a tumor necrosis factor (TNF) domain of a TRANCE protein. The specification, while enabling for the polypeptide of SEQ ID NO: 3, does not teach the identity of every possible TNF domain of TRANCE, and of every possible TNF domain-containing protein. The breadth of the claim is excessive, reading on *a TNF domain of a TRANCE protein*. The specification does not provide guidance teaching which TNF domains from which TRANCE proteins could be in the instant invention. Could TNF domains from multiple TRANCE proteins, such as human, mouse, rat, etc. be used? The specification also does not teach which particular TNF domains from TRANCE proteins are effective. Because there is no guidance or working examples in the specification, a skilled artisan would not be able to predict which TNF domains from which TRANCE proteins could be used to practice the instant invention without further undue experimentation. Furthermore, the claim encompasses any polypeptide with a TNF domain from a TRANCE protein. Such polypeptides could be the isolated TNF domain by itself, or in conjunction with virtually any other polypeptide, such as a fusion protein. Therefore, any polypeptide can theoretically be fused to the TNF domain to create a TNF domain-containing protein. The specification does not teach the identities, or provide working examples, of any TNF domain-containing proteins other than that of SEQ ID NO: 3. A person of ordinary

skill in the art would not be able to predict which possible TNF domain-containing proteins would retain the desired function of increasing TRANCE activity, and therefore would not be able to make and use all possible TNF domain-containing proteins without undue experimentation. In summary, due to the excessive breadth of the claim, and lack of guidance and working examples in the specification that teach the identities of TNF domain-containing proteins that can be used with the instant invention, and the unpredictability of the invention, a person of ordinary skill in the art would not be able to make and use the invention commensurate with the scope of the claim.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 9-10, 12-14, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 9 and 10 are discussed below. Claims 12-14 and 20 are rejected for depending from rejected base claims.

1. Claims 9 and 10 are drawn to methods of administering a TRANCE-increasing agent (claim 9), and a TRANCE-increasing agent that comprises a TNF domain-containing protein (claim 10). For reasons discussed above, claims 9 and 10 are drawn to a virtually unlimited number of polypeptides. The specification does not provide adequate written description of all possible TRANCE-increasing agents, TNF domains, and TNF domain-containing proteins. Furthermore, the specification does not adequately describe which domains, or specific residues of the domains, are critical for TRANCE function in the invention as claimed. Thus, the Applicants are claiming genii of polypeptides that are defined only by function (claim 9) or by partial structure (claim 10).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed

chemical structure of the encompassed genuses of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence of full-length TRANCE, TRAF6, or set forth in SEQ ID NO: 3, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 9-10 and 12-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson (US Patent 6,242,213). The claims of the instant application are drawn to methods of administering to a mammal a TRANCE-increasing agent effective to decrease cartilage or skeletal growth. As discussed above, a TRANCE-increasing agent can be any molecule or stimuli that increases TRANCE levels or activity, including full-length TRANCE polypeptide, or domains of TRANCE polypeptide, such as that defined by SEQ ID NO: 3. Anderson teaches a polypeptide with 100% identity to SEQ ID NO: 3 (SEQ ID NO: 13 – see attached sequence comparison). As such, it is a TRANCE-increasing agent that meets the limitations of claims 9-10 and 12-14. Anderson also teaches pharmaceutical preparations containing TRANCE polypeptides, and the administration of the TRANCE polypeptides to treat human disease (column 15, lines 28-46). Claim 9 does not further define any disease or condition to be treated by a TRANCE-increasing agent. The claim merely reads on treating "a disorder comprising excessive cartilage growth or excessive skeletal growth". As such, the claim does not limit the disease to be treated, and encompasses any disease that would be treatable by decreasing cartilage or skeletal growth. The metes and bounds of "excessive cartilage growth or skeletal growth" have not been defined. Therefore, it can be concluded for the purposes of claim interpretation with regards to applying the prior art, that any mammal may have excessive cartilage or skeletal growth (for example, a person with a bigger nose or bigger ears than desired). Although Anderson does not teach administration of TRANCE polypeptides to treat cartilage and skeletal disorders, TRANCE has been known in the art as an agent that promotes osteoclastogenesis and bone resorption (Lacey *et al*, 1998, Cell, Vol. 93, p. 165-176). Therefore, these properties would be inherent in any composition comprised of TRANCE polypeptides, and the pharmaceutical composition taught by Anderson would be capable of treating a mammal with a disorder comprised of excessive cartilage or skeletal growth. Furthermore, Lacey *et al* is not being used as grounds for rejection, but to cite an inherent property of TRANCE.

2. Claims 9-10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lacey *et al* (1998, Cell, Vol. 93, p. 165-176). Lacey *et al* teaches administration of osteoprotegrin ligand (OPGL) polypeptide to mice, resulting in increased osteoclast activation and a decrease in the bone volume compared to saline-treated mice (p. 172, 2nd column, and Figure 8). OPGL is well known in the art as a synonym for TRANCE (see Takahashi *et al*,

1999, Biochem Biophys Res Comm, Vol. 256, p. 449-455, in particular p. 451, 2nd column – p. 452, 1st column, and Figure 2); thus Lacey et al teaches that administration of TRANCE polypeptides is an effective treatment for diseases characterized by excessive cartilage or skeletal growth.

3. Claims 9-10, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Chandrasekhar et al (WO 01/23559). Chandrasekhar *et al* teach polynucleotides encoding human osteoclast differentiation factor (ODF) polypeptides. It is known in the art, as well as stated in the specification of the instant invention on p. 1, lines 27-28, that ODF and TRANCE are synonyms for the same protein. The ODF/TRANCE-encoding polynucleotides, by virtue of encoding TRANCE polypeptides, and can therefore be considered TRANCE-increasing agents. Chandrasekhar et al also teach pharmaceutical preparations and methods of delivery of the TRANCE-encoding polynucleotides (p. 45-51). Furthermore, Chandresekhar *et al* specifically teach administration of the human TRANCE-encoding polynucleotides as a method of treating diseases of the skeletal system (claims 26-27, 30, 46, and 51), thus meeting the limitations of claims 9, 10, and 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US Patent 6,242,213), and further in view of Lacey et al (1998, Cell, Vol. 93, p. 165-176). The claims of the instant invention are drawn to methods of using a TRANCE-increasing agent to treat disorders comprised of excessive cartilage or skeletal growth. Claim 20 further recites the specific disorders of acromegaly, gigantism, exostosis cartilaginea, exostosis bursata, and multiple osteocartilaginous exostoses. As discussed above, Anderson describes a TRANCE-increasing agent, and pharmaceutical preparations of the TRANCE-increasing agent, but does not specially demonstrate treatment of any disease with the pharmaceutical

composition. Lacey *et al* demonstrate that administration of TRANCE-increasing agent is capable of increasing osteoclast activation and subsequently increasing bone resorption, leading to decreased bone volume, but does not specifically demonstrate that the TRANCE-increasing agent is effective for treating the aforementioned diseases. However, Lacey et al does demonstrate that TRANCE-increasing agents are effective in treating diseases characterized by excessive cartilage or skeletal growth. Therefore, a person of ordinary skill in the art would have the both the motivation, and a reasonable expectation of success, to combine the teachings of Anderson, which describes a pharmaceutical preparation of a TRANCE-increasing agent, with the teachings of Lacey et al, to treat the diseases of claim 20, which are characterized by excessive cartilage or skeletal growth. Furthermore, a person or ordinary skill in the art would also be motivated to optimize, through routine experimentation, the administration of the TRANCE-increasing agents to local sites of excessive cartilage or skeletal growth. Such local administration is common and well-known in the art, and a skilled artisan would have both the motivation to do so, and a reasonable expectation of success in practicing the invention as claimed by doing so.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached on M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BDH
Art Unit 1646

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PRIMARY EXAMINER